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Observations arising from a Beckmann rearrangement-Mannich cyclization approach to the azepinobisindole alkaloid iheyamine A

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ABSTRACT

An overview of an iterative Beckmann rearrangement-Mannich cyclization approach to the azepinobisindole alkaloid iheyamine A is described. In a preliminary model study, the (*E*)-oxime **10** underwent Beckmann rearrangement to give the bisindolylacetamide **4** followed by an intramolecular Mannich cyclization affording 2-(indolin-2-yl)indole **5** containing the heterocyclic framework of the iheyamine alkaloids. However, the 2-(indolin-2-yl)indole **5** could not be converted into the azepinobisindole core of iheyamine A. When the same Beckmann-Mannich approach was applied toward the natural product itself, a result was obtained that contrasted the model study. The (*E*)-oxime **3** did not undergo Beckmann rearrangement, but instead an intramolecular Mannich cyclization whereby the electron rich C4 site attacked the intermediate iminum ion, generating the 4-(indolin-2-yl)indole **25** bearing the heterocyclic framework of the slime mould pigment arcyriacyanin A. Although this route did not result in the synthesis of iheyamine A being accomplished, some interesting observations related to the venerable Beckmann rearrangement and Mannich cyclization reactions are described.

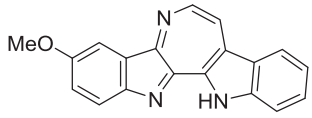
1. Introduction

Iheyamines A (**1**) and B (**2**) were isolated from the ascidian *Polycitorella* sp. collected off Iheya island, Okinawa (Fig. 1).[1] The unique azepinobisindole scaffold present in these alkaloids inspired our research group to recently complete a total synthesis of iheyamine A using a route featuring a cross-Mannich reaction to forge the 2,2′-bisindole bond.[2] Prior to this successful synthesis, a distinct synthetic route to iheyamine A was pursued, the details of which are reported herein.

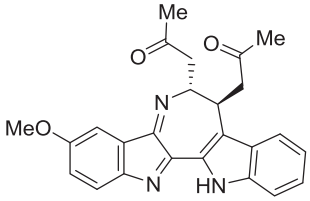
Our initial plan was to develop a procedure to simultaneously integrate nitrogen into the indole 3-position and build the azepine heterocycle in a one-pot operation (Scheme 1). Along these lines, it was predicted that under acidic conditions, (*E*)-oxime **3** would undergo a stereospecific Beckmann rearrangement[3] to form bisindolylacetamide **4** followed by an intramolecular Mannich cyclization[4,5] to give the 2-(indolin-2-yl)indole **5**. Given that **5** contained the complete skeleton of iheyamine A, its subsequent transformation into the natural product was predicted to require facile redox chemistry. The route in Scheme 1 depicts the Beckmann rearrangement occurring first; the process could also commence with a Mannich cyclization followed by an intramolecular Beckmann rearrangement.

2. Results and discussion

In order to gauge the viability of the proposal outlined in



iheyamine A



iheyamine B

Fig. 1. Iheyamines A (**1**) and B (**2**).

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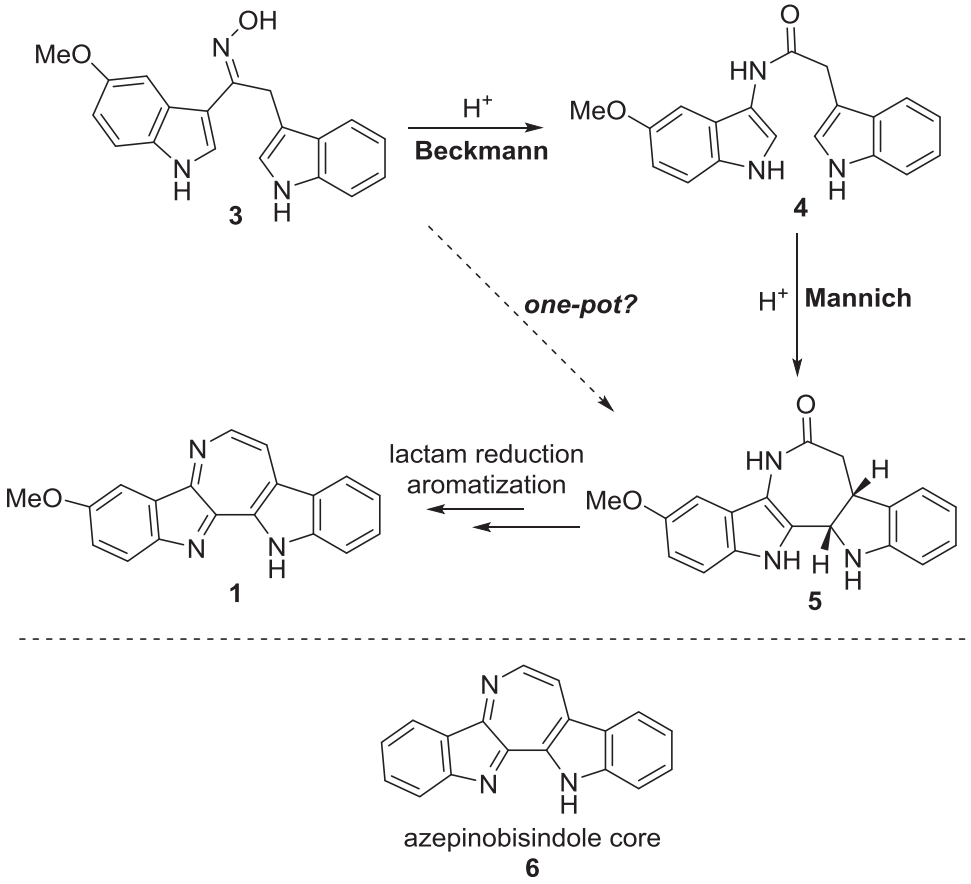
Scheme 1, a model study was initiated targeting the azepinobisindole core **6** of iheyamine A (Scheme 2). The known bis(indolyl) ketone **7**[6] was converted to the thermodynamically favoured (*E*)-**8**, with the oxime geometry confirmed by NOE analysis.[7] Given that both the Beckmann rearrangement and Mannich cyclization can be promoted by TFA,[3,4,8] we subjected (*E*)-**8** to TFA at room temperature in an effort to effect the proposed Beckmann-Mannich cascade, which led to the bisindolylacetamide **9** rapidly being formed. The product **9** is a result of the Beckmann rearrangement proceeding with the desired regioselectivity (migration of the *anti*-indole heterocycle), as confirmed by NOE analysis.[7] Upon subjecting the bisindolylacetamide **9** to TFA at 100 °C, the intramolecular Mannich reaction occurred to give the desired 2-(indolin-2-yl)indole **10**. Somewhat disappointingly, although the Beckmann rearrangement and Mannich cyclization both proceeded in neat TFA, we were unable to effect both of these reactions in a one-pot operation. For example, when the oxime **8** had undergone Beckmann rearrangement to **9** (as indicated by TLC analysis), heating the reaction to initiate the Mannich cyclization led to degradation.

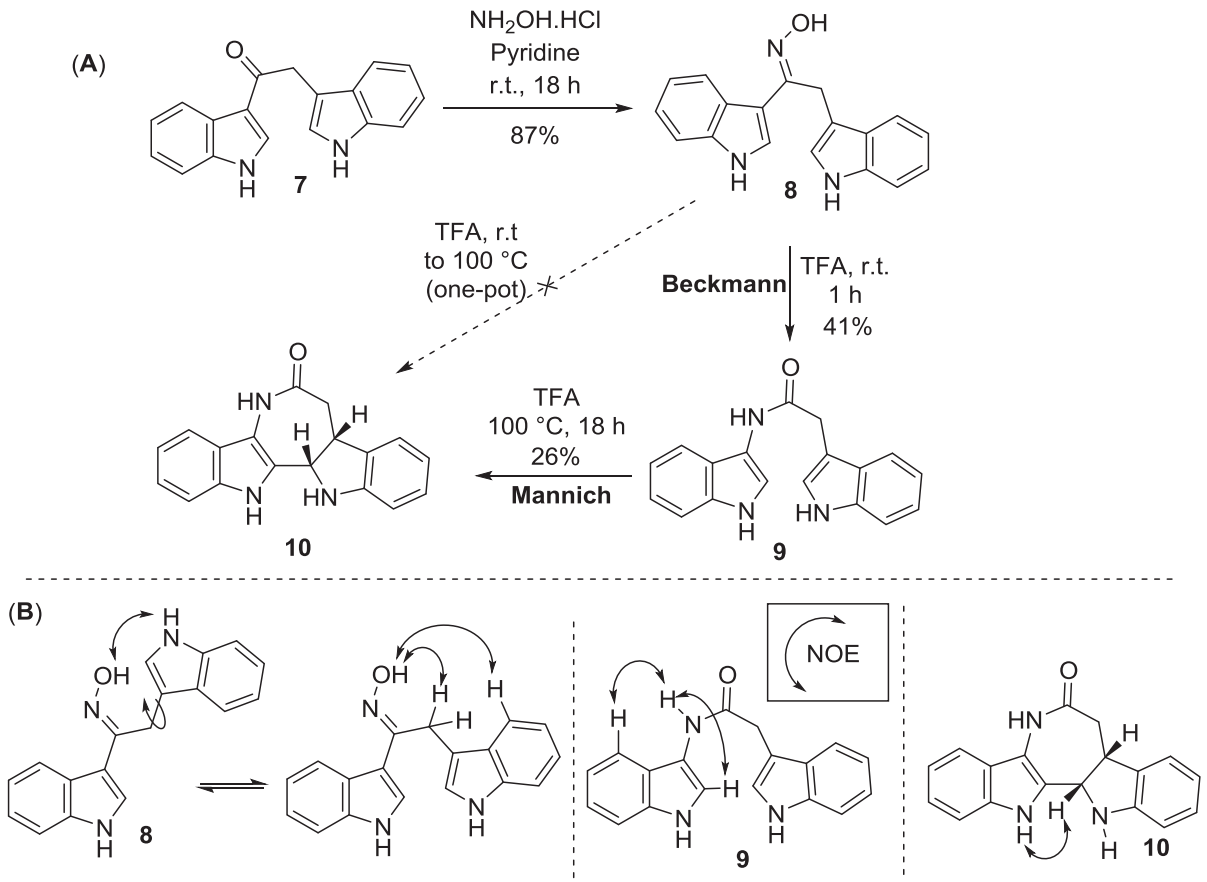
The desired regiochemical outcome for the Mannich reaction (**9** to **10**) is worthy of comment and can be attributed to the choice of an amide (**9**) as the substrate for this reaction. This feature of the synthetic plan was guided by Bremner and co-workers' attempted biomimetic synthesis of the *N*-methyl iheyamine A core **11** (Scheme 3, **A**).[9] Bremner's approach required C–C bond migration to occur during the acid-mediated Plancher rearrangement[10,11] of spirocycle **11**, generating the carbocation **12** and hence the desired *N*-methylazepinobisindole **13**. However, C–N bond migration was favoured, resulting in the isomeric azepinobisindole **15**. In this instance, we posit the C–C bond migration did not occur as carbocation **12** is not resonance stabilised by the adjacent amine, which would be protonated under the reaction conditions. Conversely, C–N bond migration generated carbocation **14** stabilised by two aromatic systems. In our approach (Scheme 3, **B**), protonation of bisindolylacetamide **9** initiated an intramolecular Mannich cyclization to give the spirocycle **16** analogous to Bremner's intermediate **11**. In this instance, **16** undergoes C–C bond migration to give the desired 2-(indolin-2-yl)indole **10** via the carbocation **17**, which would experience resonance stabilization from the adjacent amide. C–N bond migration in **16** is also less favoured as carbocation **18** is only stabilised by one indole (compared to two in carbocation **14**) and as such, the undesired regioisomer **19** was not observed.

With the complete heterocyclic framework of the iheyamines assembled, we set out to convert 2-(indolin-2-yl)indole **10** into the azepinobisindole **6** using standard redox transformations (Scheme 4). This proved much harder than anticipated; attempted reduction of the lactam in **10** failed to give **20** when using a variety of reducing agents including lithium aluminium hydride, diisobutylaluminium hydride, borane and alane, a result that was attributed to the instability of compound **10**. It was thought that dehydrogenation of the indoline in **10** would give a more stable 2,2′-bisindole **21**, that upon lactam reduction would enable access to the azepinobisindole **6**. Despite careful treatment of **10** with one equivalent of DDQ, we were unable to prevent **22** being rapidly formed as a result of facile aromatization; the 2,2′-bisindole **21** was never observed. Subjecting **22** to the reducing agents described previously led to degradation and all attempts to access **6** from **22** via the imidoyl chloride[12] also failed.

The Beckmann-Mannich approach toward the synthesis of



Scheme 1. Proposed Beckmann-Mannich approach to iheyamine A (**1**).



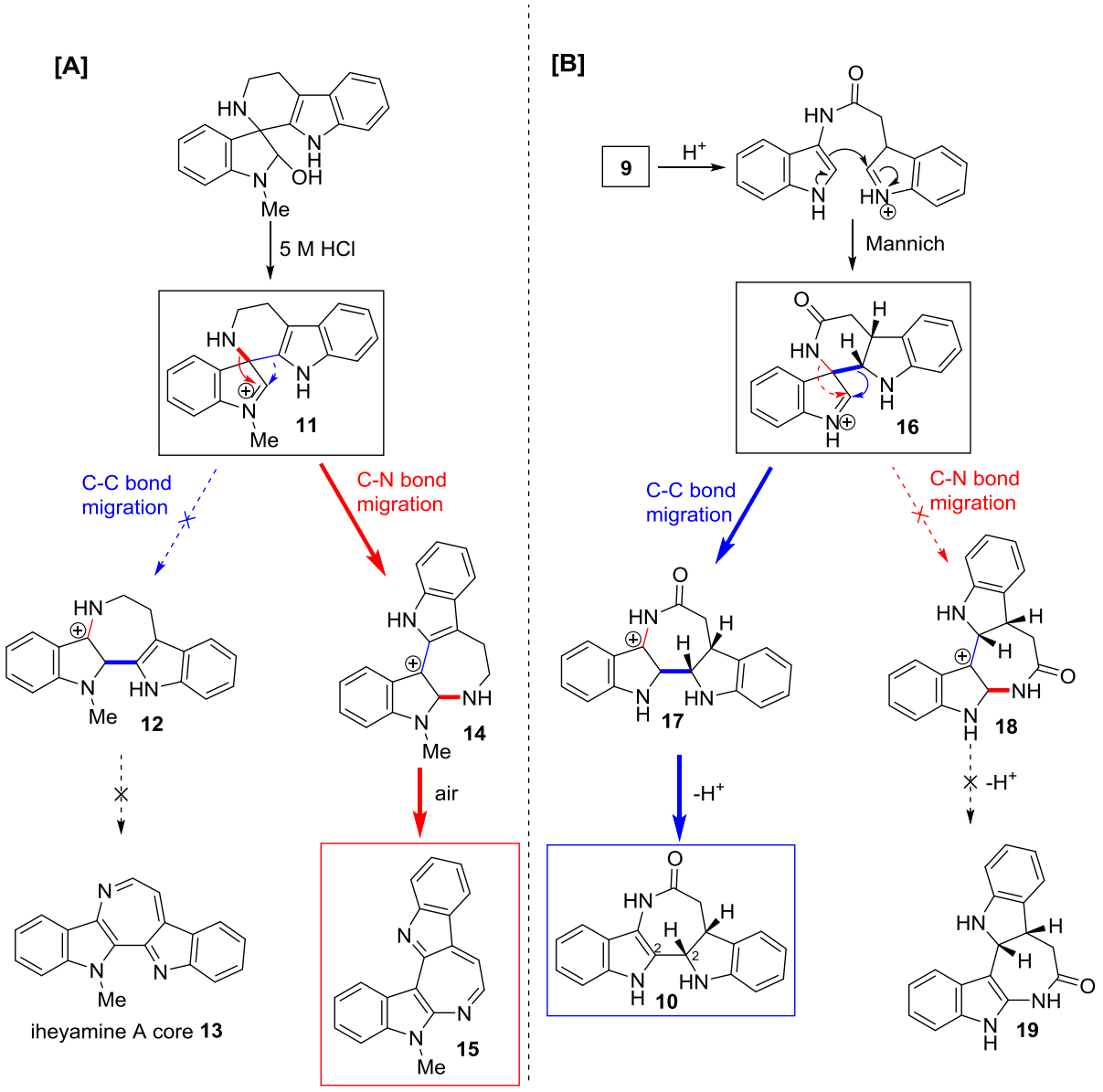
Scheme 2. [**A**] Synthesis of 2-(indolin-2-yl)indole **10** by sequential Beckmann rearrangement-Mannich cyclization; [**B**] key NOE correlations in **8**, **9** and **10**.

iheyamine A was undertaken regardless of its failure on a model system (Scheme 5). Indole-3-acetic acid (IAA) was converted to the acid chloride that was added to a freshly prepared solution of 5-methoxyindolylmagnesium bromide to give the unstable bis(indolyl)ketone **24**, which was readily transformed into (*E*)-oxime **3**, the geometry of which was confirmed by NOE analysis.[8] Although the yield of **3** is only 15% from IAA, greater than 500 mg batches of **3** could be quickly prepared. It was assumed that **3** would undergo a Beckmann rearrangement in an analogous fashion to the model study and provide bisindolylacetamide **4**. Upon subjecting oxime **3** to TFA at room temperature, the reaction was much slower than in the model study (18 h vs 1 h). A single product was formed, but it was readily apparent that it was not the bisindolylacetamide **4**. A sharp singlet at in the ^{1}H NMR spectrum at 10.54 ppm inferred the oxime was still present. Furthermore, the ^{1}H NMR spectrum contained peaks indicative of an indoline, suggesting a Mannich cyclization had occurred. However, the indole C2–H peak was still present in the ^{1}H NMR spectrum, suggesting the product was 4-(indolin-2-yl)indole **25**, which was subsequently confirmed by X-ray analysis (Fig. 2).[13] Interestingly, compound **25** possesses the same heteroaromatic framework present in the slime mould pigment arcyriacyanin A,[14] an inhibitor of protein tyrosine kinase and protein kinase C. The transformation of **3** into **25** is postulated to be the first reported intramolecular formation of a 2,4′-bisindole bond.[15]

The formation of 4-(indolin-2-yl)indole **25** is rationalised in Scheme 6. Protonation of **3** generates iminium ion **26** which could feasibly proceed through two separate mechanistic pathways. Direct attack from the electron rich C4 site (path A) would give the product **25** via **27**. In Path B, attack by the indole C3 would form the spirocyclic intermediate **28**, which following rearrangement generates the 4-(indolin-2-yl)indole **25**. Szántay and co-workers have proposed that the synthesis of azepino[5,4,3-*cd*]indoles from tryptamines and formaldehyde follows the latter mechanism.[16]

3. Conclusions

To conclude, an overview of a Beckmann rearrangement-Mannich cyclization approach towards iheyamine A is presented. In a preliminary model study targeting the azepinobisindole core of the natural product, the (*E*)-oxime **10** underwent a stereoselective Beckmann rearrangement to give the bisindolylacetamide **4** followed by an intramolecular Mannich cyclization to give the 2-(indolin-2-yl)indole **5** containing the complete heterocyclic framework of the iheyamines. Unfortunately, the 2-(indolin-2-yl) indole **5** could not be converted into the azepinobisindole core of iheyamine A despite attempting several different redox transformations. When the same Beckmann-Mannich approach was applied to the natural product itself, a result that contrasted the model study was obtained. The (*E*)-oxime **3** did not undergo Beckmann rearrangement, but instead an intramolecular Mannich cyclization whereby the electron rich C4 site attacked the intermediate iminum ion, generating the 4-(indolin-2-yl)indole **25** bearing the scaffold present in the slime mould pigment arcyriaflavin A. Although these studies did not result in a successful synthesis of iheyamine A, the results we encountered ultimately guided the subsequent total synthesis of iheyamine A.[2]



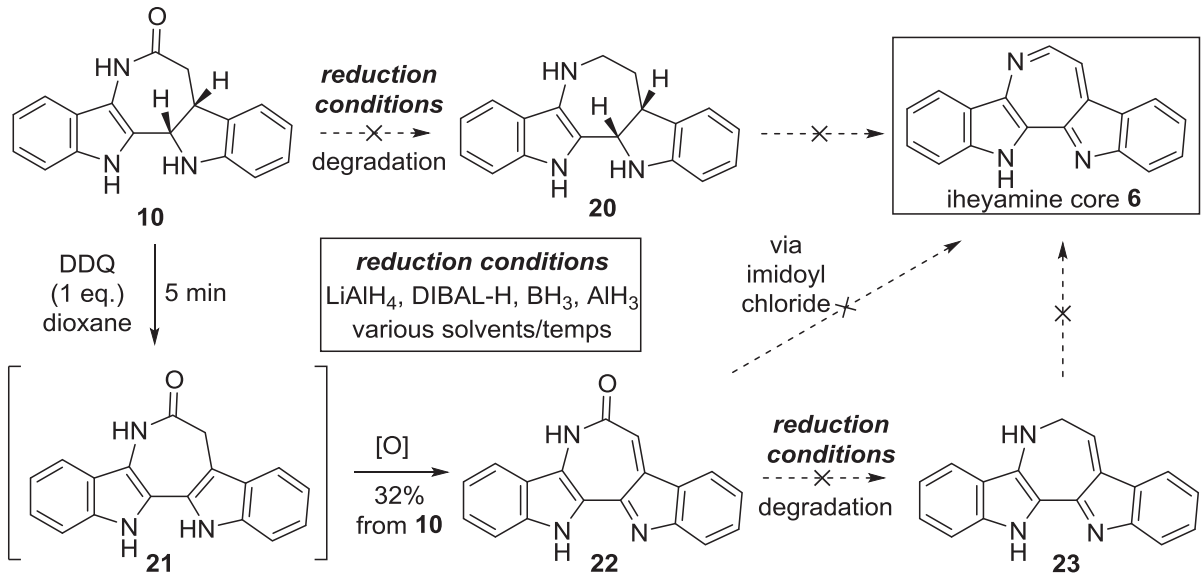
Scheme 3. [**A**] C–N bond migration in **11**[9]; [**B**] C–C bond migration in **16**.

3.1. Experimental section

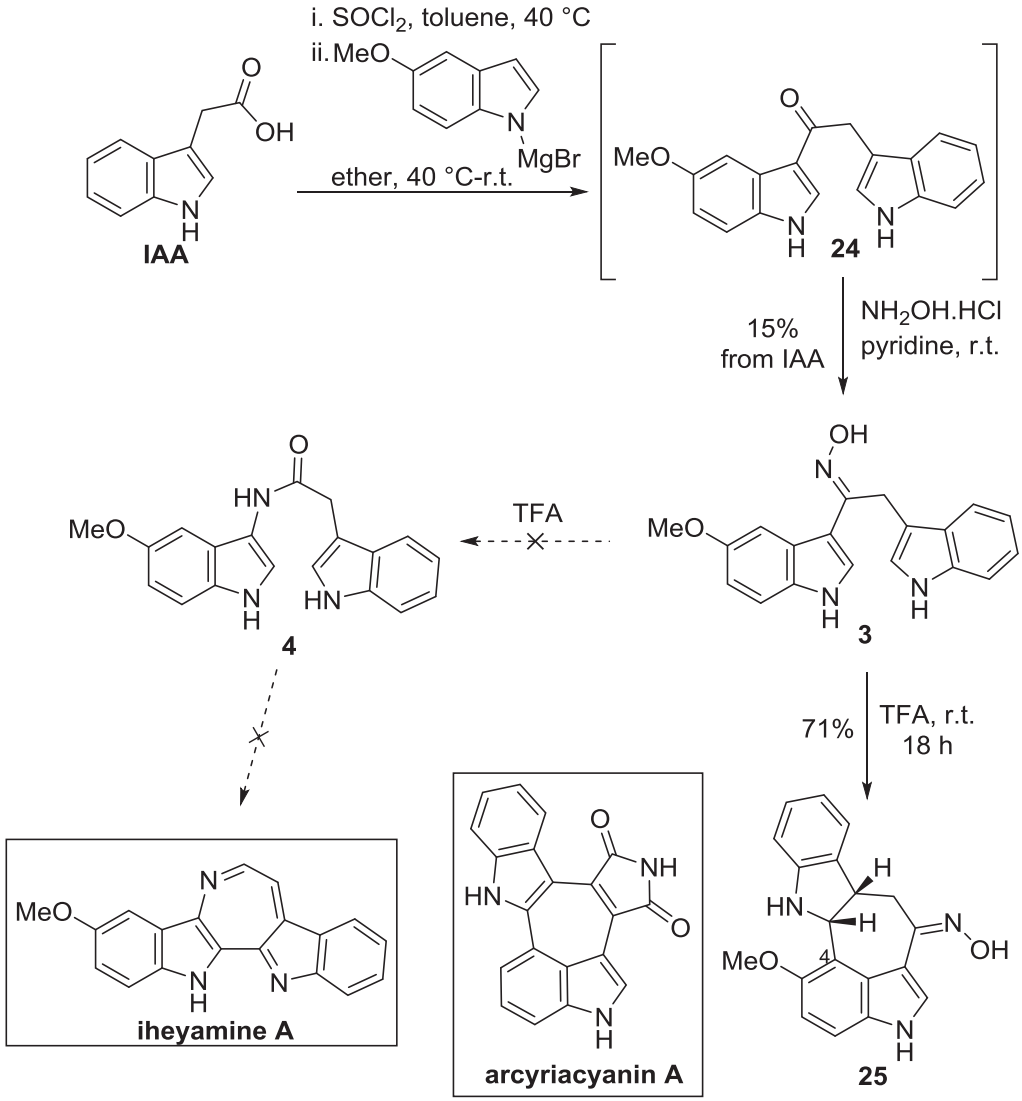
All reactions were carried out in oven-dried glassware under a nitrogen atmosphere unless otherwise stated. Analytical thin layer chromatography was performed using 0.2 mm silica plates and compounds were visualized under 365 nm ultraviolet irradiation followed by staining with either alkaline permanganate or ethanolic vanillin solution. Melting points were recorded on a melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer using a diamond ATR sampling accessory and absorption maxima are expressed in wavenumbers (cm^{-1}). NMR spectra were recorded as indicated on an NMR spectrometer operating at 500, 400 and 300 MHz for ^{1}H nuclei and 125, 100 and 75 MHz for ^{13}C nuclei. Chemical shifts are reported in parts per million (ppm) relative to the tetramethylsilane peak recorded as δ 0.00 ppm in $CDCl_3$/TMS solvent, or the residual acetone (δ 2.05 ppm), chloroform (δ 7.24 ppm), DMSO (δ 2.50 ppm) or methanol (δ 3.31 ppm) peaks. The ^{13}C NMR values were referenced to the residual acetone (δ 29.9 ppm) chloroform (δ 77.1 ppm), DMSO (δ 39.5 ppm) or methanol (δ 49.0 ppm) peaks. ^{13}C NMR values are reported as chemical shift δ and assignment. ^{1}H NMR shift values are reported as chemical shift δ, relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (J in Hz) and assignment. Assignments are made with the aid of DEPT 90, DEPT 135, COSY, NOESY and HSQC experiments. High resolution mass spectra were obtained by electrospray ionization in positive ion mode at a nominal accelerating voltage of 70 eV on a microTOF mass spectrometer.

3.1.1. *(E)-1,2-Di(indol-3-yl)ethanone oxime (**8**)*

Hydroxylamine hydrochloride (65 mg, 0.94 mmol) was added to a stirred solution of bis(indolyl)ketone **7**[6] (87 mg, 0.32 mmol) in pyridine (1 mL) and the resulting mixture was stirred at r.t. for 18 h. Ethyl acetate (20 mL) was added and the mixture washed with copper sulfate solution (10% aq., 5 × 20 mL). The organic extract was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel eluting with hexanes-ethyl



Scheme 4. Attempted conversion of **10** into azepinobisindole **6**.



Scheme 5. Unexpected formation of **25** from oxime (*E*)-**3**.

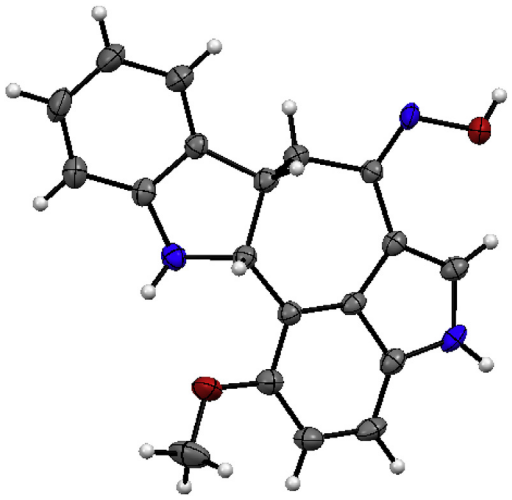


Fig. 2. ORTEP representation of **25**.[13]

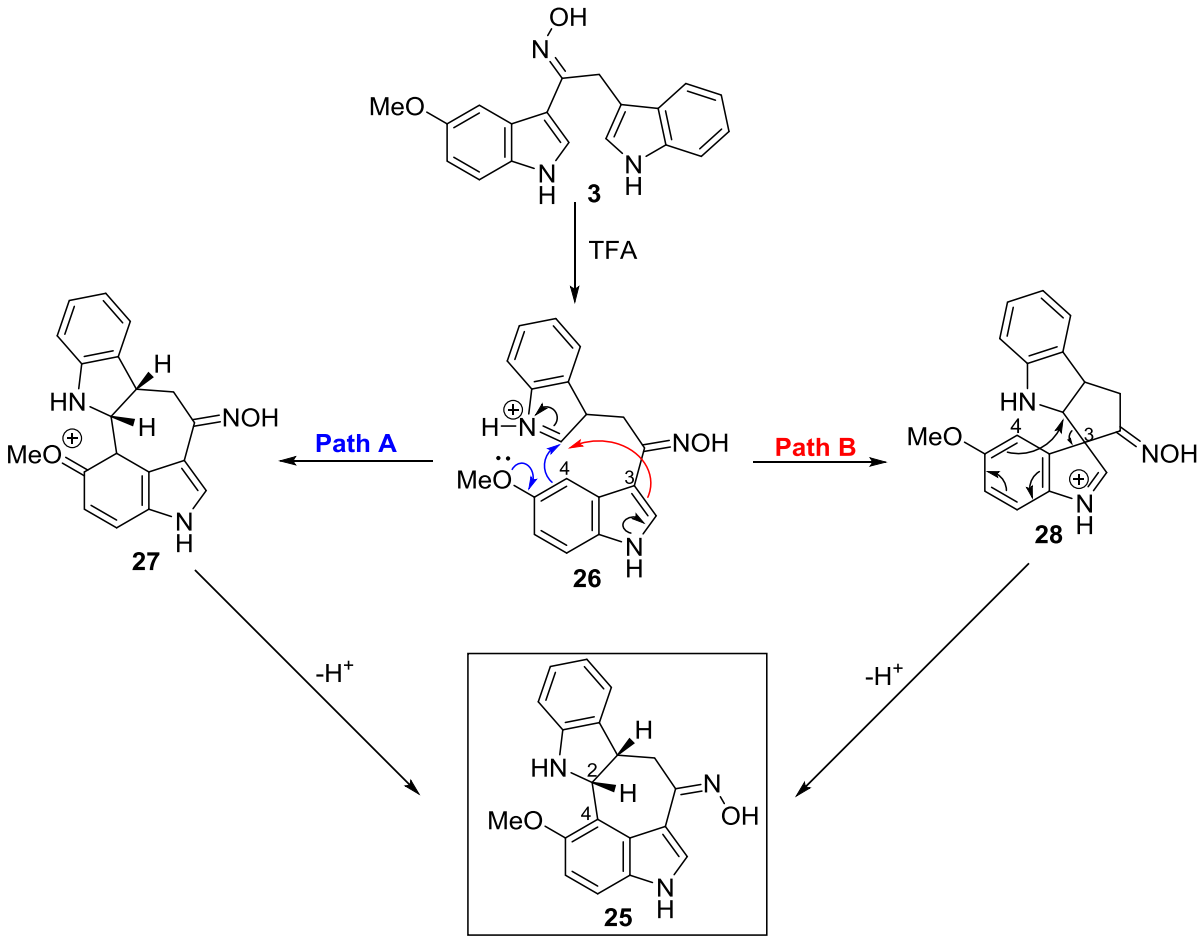
acetate (1:1) gave the *title compound* (79 mg, 0.27 mmol, 87%) as a brown solid, M.p. 179.5–181.8 °C (charred); HRMS [ESI, $(M + H)^+$] found 290.1281 [$C_{18}H_{15}N_3O + H]^+$ requires 290.1288; ν_{max}/cm^{-1} (neat) 3395, 3057, 1705, 1241, 1043; δ_H (400 MHz, $(CD_3)_2SO$) 11.20 (1 H, br s, NH), 10.75 (1 H, br s, NH), 10.74 (1 H, s, OH), 8.15 (1 H, d, *J* 8.1, CH), 7.79 (1 H, d, *J* 8.1, CH), 7.74 (1 H, d, *J* 2.8, CH), 7.35 (1 H, d, *J* 7.8, CH), 7.30 (1 H, d, *J* 7.8, CH), 7.17 (1 H, d, *J* 2.3, CH), 7.11–7.00 (3 H, m, 3 × CH), 6.96 (1 H, t, *J* 7.5, CH), 4.18 (2 H, s, CH_2); δ_C (100 MHz, $(CD_3)_2SO$) 153.7 (C), 136.7 (C), 135.9 (C), 127.1 (C), 126.4 (CH), 124.7 (C), 123.5 (CH), 122.5 (CH), 121.7 (CH), 120.7 (CH), 119.6 (CH), 118.8 (CH), 118.1 (CH), 112.2 (C), 111.4 (CH), 111.2 (CH), 111.0 (C), 21.7 (CH_2).

3.1.2. *N,2-Di(indol-3-yl)acetamide (**9**)*

A solution of oxime **8** (252 mg, 0.87 mmol) in trifluoroacetic acid (2 mL) was stirred for 1 h at r.t. The reaction mixture was diluted with ethyl acetate (20 mL), washed with saturated sodium hydrogen carbonate (3 × 20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel eluting with hexanes-ethyl acetate (1:1) gave the *title compound* (102 mg, 0.35 mmol, 41%) as a pale orange oil. HRMS [ESI, $(M + Na)^+$] found 312.1109 [$C_{18}H_{15}N_3O + Na]^+$ requires 312.1107; ν_{max}/cm^{-1} (neat): 3395, 1892, 1702, 1419; δ_H (400 MHz, $(CD_3)_2SO$) 11.38 (1 H, br s, NH), 10.65 (1 H, br s, NH), 10.61 (1 H, br s, NH), 7.96 (1 H, d, *J* 2.6, CH), 7.72 (1 H, d, *J* 8.1, CH), 7.65 (1 H, d, *J* 8.1, CH), 7.35 (1 H, d, *J* 8.0, CH), 7.27 (1 H, d, *J* 8.0, CH), 7.07–7.01 (2 H, m, 2 × CH), 6.98–6.92 (3 H, m, 3 × CH), 4.10 (2 H, s, CH_2); δ_C (100 MHz, $(CD_3)_2SO$) 149.7 (C), 136.1 (C), 135.6 (C), 128.7 (CH), 127.4 (C), 125.6 (C), 123.0 (CH), 122.1 (CH), 121.0 (CH), 120.8 (CH), 119.1 (CH), 118.7 (CH), 118.2 (CH), 111.5 (C), 111.4 (CH), 111.2 (CH), 108.5 (C), 31.2 (CH_2).

3.1.3. *(±)-7,7a,12,12a-Tetrahydro-5H-azepino[3,2-b:4,5-b′]diindol-6(13H)-one (**10**)*

A solution of bisindolylacetamide **9** (84 mg, 0.3 mmol) in trifluoroacetic acid (2 mL) was stirred at 100 °C for 18 h. The reaction



Scheme 6. Mechanistic considerations for the formation of 4-(indolin-2-yl)indole **25**.

was cooled, diluted with ethyl acetate (10 mL) and carefully neutralised with saturated sodium hydrogen carbonate (20 mL). The organic phase was washed with saturated sodium hydrogen carbonate (3 × 20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel eluting with ethyl acetate-hexanes (1:1) gave the *title compound* (22 mg, 0.08 mmol, 26%) as a brown oil. HRMS [ESI, $(M + Na)^+$] found 312.1118 $[C_{18}H_{15}N_3O + Na]^+$ requires 312.1107; ν_{max}/cm^{-1} (neat) 3240, 2924, 1682, 1454, 740; δ_H (400 MHz, $(CD_3)_2CO$) 10.33 (1 H, br s, NH), 9.65 (1 H, s, NH), 7.98 (1 H, d, *J* 7.9, CH), 7.34 (1 H, dd, *J* 7.9, 0.8, CH), 7.16 (1 H, d, *J* 7.0, CH), 7.12–7.09 (1 H, m, CH), 7.03–6.99 (1 H, m, CH), 6.92–6.88 (1 H, m, CH), 6.64 (1 H, t, *J* 7.0, CH), 6.54 (1 H, d, *J* 7.9, CH), 5.40 (1 H, br s, NH), 5.06 (1 H, d, *J* 7.9, CH), 3.86–3.83 (1 H, m, CH), 3.53 (1 H, dd, *J* 17.0, 5.4, CH_2), 2.96 (1 H, dd, *J* 17.0, 5.4, CH_2); δ_C (100 MHz, $(CD_3)_2CO$) 148.9 (C), 128.5 (CH), 126.1 (CH), 123.9 (CH), 123.2 (CH), 123.1 (CH), 120.94 (2 × C), 120.90 (C), 119.32 (C), 119.30 (C), 119.2 (C), 111.9 (CH), 110.4 (2 × CH), 60.5 (CH), 41.7 (CH), 23.8 (CH_2).

3.1.4. 5H -Azepino[3,2-b:4,5-b′]diindol-6(13H)-one (**22**)

To a solution of 2-(indolin-2-yl)indole **10** (23 mg, 0.08 mmol) in dioxane (1 mL) at 0 °C was carefully added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (17 mg, 0.07 mmol) portionwise. The resulting reaction mixture was warmed to r.t. and stirred for 5 min, then diluted with ethyl acetate (10 mL). The organic phase was washed with saturated sodium hydrogen carbonate (5 × 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel eluting with ethyl acetate-hexanes (2:1) gave the *title compound* (7 mg, 0.02 mmol, 32%) as a red solid, M.p. 270.2–274.5 °C; HRMS [ESI, $(M + H)^+$] found 286.0977 $[C_{18}H_{11}N_3O + H]^+$ requires 286.0975; ν_{max}/cm^{-1} 3373, 2955, 2916, 2166, 1736; δ_H (400 MHz, $(CD_3)_2SO$) 11.95 (1 H, br s, NH), 11.70 (1 H, br s, NH), 8.91 (1 H, d, *J* 8.0, CH), 8.41 (2 H, d, *J* 8.0, 2 × CH), 7.86–7.82 (2 H, t, *J* 9.2, 2 × CH), 7.61–7.53 (2 H, m, 2 × CH), 7.39–7.31 (2 H, m, 2 × CH); δ_C (100 MHz, $(CD_3)_2SO$) 177.7 (C), 152.8 (C), 140.32 (C), 140.29 (C), 126.7 (CH), 126.6 (CH), 125.21 (C), 125.18 (C), 124.4 (CH), 122.8 (C), 122.2 (C), 121.1 (CH), 121.0 (C), 120.9 (2 × CH), 119.9 (CH), 112.8 (CH), 112.2 (CH).

3.1.5. (E)-2-(Indol-3-yl)-1-(5-methoxyindol-3-yl)ethanone oxime (**3**)

Thionyl chloride (0.83 mL, 11.43 mmol) was added dropwise to a stirred suspension of indole-3-acetic acid (IAA, 2 g, 11.4 mmol) in toluene (20 mL) at r.t. The reaction mixture was stirred at r.t. for 30 min, 40 °C for 1.5 h, cooled to r.t. and concentrated *in vacuo* to give indole-3-acetyl chloride.

To a solution of methylmagnesium bromide (3.4 mL, 1 M in THF) in ether (10 mL) at r.t was added a solution of 5-methoxyindole (1.5 g, 10.2 mmol) in ether (10 mL) dropwise. The reaction mixture was cooled to −10 °C and a solution of indole-3-acetyl chloride in ether (20 mL) was added quickly in one portion. The reaction mixture was warmed to r.t. and stirred for 16 h. Water (100 mL) was added and the mixture extracted with ethyl acetate (3 × 100 mL). The organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel eluting with hexanes-ethyl acetate (1:1) gave the ketone **24** (731 mg, 2.85 mmol, 25%) as a brown solid that was used immediately in the next step.

Hydroxylamine hydrochloride (500 mg, 7.2 mmol) was added to a stirred solution of bis(indolyl)ketone **22** (731 mg, 2.85 mmol) in pyridine (10 mL) and the reaction mixture stirred at r.t. for 18 h. Ethyl acetate (50 mL) was added and the mixture washed with a solution of copper sulfate (10%; 5 × 50 mL). The organic extract was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel eluting with hexanes-ethyl acetate (1:1) gave the *title compound* (584 mg, 1.72 mmol, 16% from IAA) as a brown solid, M.p. 184.4–185.8 °C; HRMS [ESI, $(M + Na)^+$] found 342.1211 $[C_{19}H_{17}N_3O_2 + H]^+$ requires 342.1213; ν_{max}/cm^{-1} (neat) 3402. 2914, 1620, 1484, 1423; δ_H (400 MHz, $(CD_3)_2SO$) 11.07 (1 H, br s, NH), 10.74 (1 H, br s, NH), 10.69 (1 H, s, OH), 7.78 (1 H, d, *J* 8.0, CH), 7.70 (1 H, d, *J* 2.7, CH), 7.66 (1 H, d, *J* 2.7, CH), 7.31 (1 H, d, *J* 8.0, CH), 7.26 (1 H, d, *J* 8.8, CH), 7.15 (1 H, d, *J* 2.2, CH), 7.03–7.01 (1 H, m, CH), 6.97–6.95 (1 H, m, CH), 6.75 (1 H, dd, *J* 8.8, 2.7, CH), 4.16 (2 H, s, CH_2), 3.73 (3 H, s, Me); δ_C (100 MHz, $(CD_3)_2SO$) 153.9 (2 × C), 135.9 (C), 131.7 (C), 127.1 (C), 127.0 (CH), 125.1 (C), 123.5 (CH), 120.7 (CH), 118.8 (CH), 118.1 (CH), 112.0 (CH), 111.9 (C), 111.8 (CH), 111.2 (CH), 111.0 (C), 104.3 (CH), 55.3 (Me), 21.7 (CH_2).

3.1.6. (±)-10-Methoxy-4,4a,9,9a-tetrahydrocyclohepta[1,2-b:5,6,7-c′d′]diindol-3(1H)-one oxime (**25**)

A solution of oxime **3** (189 mg, 0.529 mmol) in trifluoroacetic acid (4 mL) was stirred at r.t. for 18 h. The reaction mixture was carefully neutralised (sat. sodium hydrogen carbonate) and extracted with ethyl acetate (3 × 10 mL). The organic extracts were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel eluting with toluene-acetone (7:3) gave the *title compound* (134 mg, 0.42 mmol, 71%) as a brown solid, M.p. 156.1–159.3 °C (charred); HRMS [ESI, $(M + Na)^+$] found 342.1219 $[C_{19}H_{17}N_3O_2 + H]^+$ requires 342.1213; ν_{max}/cm^{-1} (neat) 3147, 3048, 1608, 1461, 1227; δ_H (400 MHz, $(CD_3)_2SO$) 11.48 (1 H, br s, NH), 10.54 (1 H, s, OH), 8.39 (1 H, d, *J* 3.0, CH), 7.41 (1 H, d, *J* 8.7, CH), 7.18 (1 H, d, *J* 7.5, CH), 7.04 (1 H, d, *J* 8.7, CH), 6.96 (1 H, t, *J* 7.5, CH), 6.70–6.63 (2 H, m, 2 × CH), 5.60 (1 H, d, *J* 2.6, CH), 5.17 (1 H, dd, *J* 7.1, 2.6, CH), 3.90 (3 H, s, Me), 3.49 (1 H, t, *J* 8.0, CH_2), 2.98 (1 H, dd, *J* 14.0, 10.5, CH_2), 1 × NH not observed; δ_C (100 MHz, $(CD_3)_2SO$) 153.0 (C), 150.4 (C), 148.7 (C), 131.3 (CH), 130.8 (C), 128.9 (C), 128.2 (C), 127.0 (CH), 124.1 (C), 123.7 (CH), 117.9 (CH), 111.1 (CH), 109.3 (CH), 107.6 (C), 107.4 (CH), 61.4 (CH), 56.5 (Me), 43.4 (CH), 36.3 (CH_2).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2017.05.093.

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